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The University of Toronto Medical Journal

VOL. I

MARCH, 1924

No. 4

EDITORIAL

SIR WILLIAM JENNER once enumerated to a friend the qualities which he considered to be essential in a medical man. "He needs", said the great physician, "three things. He must be honest, he must be dogmatic, and he must be kind". Just how far one should be dogmatic is a question which puzzles many students in medicine. They are at a loss sometimes to account for the changing interpretations in many of the problems of disease, for the apparent variation in the views which different clinicians present to them. They are not at all sure of the attitude which they should have towards what may be termed facts, and much less certain how they should regard the current explanations of those facts. The answer to all these questions involves our conception of the nature of science.

Dr. Jacks of the *Hibbert Journal* has recently turned his kindly philosophic eye upon the scientific field and in an article dealing with the proper attitude towards science makes some observations upon facts and scientific truths and their interpretation. Facts, he says, however complacent we may feel about them, are not absolute. Neither are they poor things to be exploited as we see fit, but they are to be revered because each one contains a bit of reality. While they must not be regarded as final, they are still challenging because after all nothing is quite so mysterious as a fact. There is not a single fact in nature, the whole truth of which is known to anyone.

This being the case, science is essentially that which moves. In its task of discovering the universe (not explaining it) it is never content with the boundary which it has reached. In Dr. Jack's words, "Science abhors a limitation as fiercely as nature abhors a vacuum". The changing theories, therefore, which one encounters in the course of his studies may be regarded as in the very nature of scientific progress.

There is a limitation in science, however, as Dr. Jacks points out, and that in the use to which its truths may be put. Neither a great collection of scientific truths nor the facts of a hundred sciences make for safety. Truth is at once "the most splendid and dangerous thing in the universe", and the test of the soundness of one's position lies in the use one is making of the knowledge which he possesses. The final limitation of natural science, approaching it from the human side, Dr. Jacks concludes, lies in the fact that it stops short at the point where the choice has to be made between the right and the wrong application of its truths.

Every new statement of truth thrusts our life forward into new conditions, and it is at this point of responsibility that Jenner's first quality of honesty in the ideal physician has its supreme application.

HOW often, in examining a patient's hands, have we found "clubbed fingers", made a mental note of the probability that the condition is pulmonary or cardiac and have given no thought to what might cause the clubbing? In a recent issue of the *British Medical Journal* appears an interesting article by David Campbell of Glasgow on these so-called Hippocratic fingers. In his opening remarks he calls attention to the paucity of clubbed fingers that have been examined microscopically. Observers who have sectioned such fingers seem only able to agree that there is no alteration in the bone. Their ideas as to the morbid anatomy of the soft parts are as divergent as their nationalities, and at that, more is known of the morbid anatomy than of the mechanism of production of the condition. Although Campbell's paper is based on the microscopic examination of one case, nevertheless he has made a wide study of the literature on the subject. He claims that in his section the underlying pathological basis is oedema. The picture shows wide separation of the normally compact bundles of connective tissue fibrils, no fibrous thickening of the rete mucosum, no dilatation of the capillary loops under the nail, no increase in connective tissue and no excessive fat. Other writers, at various times, have claimed to have found one or other of the above and have blamed them in turn for the production of Hippocratic fingers.

In support of the oedema theory, in which he says the oedema lies between the nail bed and the bone, Campbell cites the transient nature of the clubbing as has been reported from time to time in the literature, and quotes cases of pneumonia and empyema in which such a condition obtained. Furthermore, cases in which there is definite obstruction to the venous return in the arms exhibit clubbed fingers.

In diseases of the lungs and pleura showing this condition there is no mechanical interference with the return circulation, but all pulmonary diseases have one thing in common—a definite, though varying, amount of lung substance has ceased to fulfil its proper function, and thus the oxygen tension of the blood is lowered. This can be shown to produce a defect in tissue respiration, of varying degrees of severity, and the place where this defect will be most prominent will be where the circulation is slowest, in the fingers, toes, and nose. Thus cyanosis may sometimes be detected under the finger nails in pneumonia before it is demonstrable anywhere else in the body. On the above, and on the fact that oedema is associated with conditions of imperfect oxidation, Campbell advances the theory originally conceived by Pigeaux in 1832. He meets the statements of other pathological findings on microscopic examination by indicating that other morbid changes will be brought about if the condition of oedema persists. The subject makes an interesting, if unimportant, topic of speculation.

A DISEASE, new to us on the American continent, has appeared in our midst. It is one of the dermatitis venenata group, which embodies the dermatitides caused by chemical agents, and in this particular form the visitant lurks in the lacquer of the beautifully decorated Mah Jongg boxes which are rapidly flooding the country. Two cases were recently reported in the *J.A.M.A.* Toyama blames an acid glucoside, *Rhus vernix*, the principal ingredient in Japanese lacquer, for the trouble. Symptoms appear within a few hours to a week after exposure, ranging from a simple erythema, to swelling, oedema, vesicles

MEDICAL JOURNAL

and bullae. After a few days, the erythema diminishes, the vesicles either rupture or dessicate and form crusts, and desquamation occurs. Usually at the end of two or three weeks all evidence of inflammation disappears. In the treatment the chemical must be neutralized with an alkaline wet dressing, the chemical removed, and a soothing preparation applied.

IN the last issue of the JOURNAL an article appeared discussing the possibility of present day evolution of man. The distinguishing characteristics of man are due to the enormous development of his cerebral hemispheres. A possible course of the evolution of these is given by Prof. C. Judson Herrick of the University of Chicago in a paper entitled "A Sketch of the Origin of the Cerebral Hemispheres".

It seems to be established that early in vertebrate evolution the terminal portion of the neural tube gave rise to two pairs of lateral evaginations in correlation with the differentiation of the two sense organs which serve as the most important distance receptors, namely, the optic vesicles and the olfactory bulbs. In the most primitive forms almost all that portion of the brain corresponding to the cerebrum in man was dominated by the olfactory system. As the other sense organs began to play a greater part in the life of the animals there had to be a correlation between them and the olfactory system. These functional relationships were brought about by structural variations which took place most markedly in the olfactory area where separate correlation centres for each new reflex pattern were evolved. Thus what was first an almost purely olfactory area comes to be dominated by whatever sense system is most used in a particular environment.

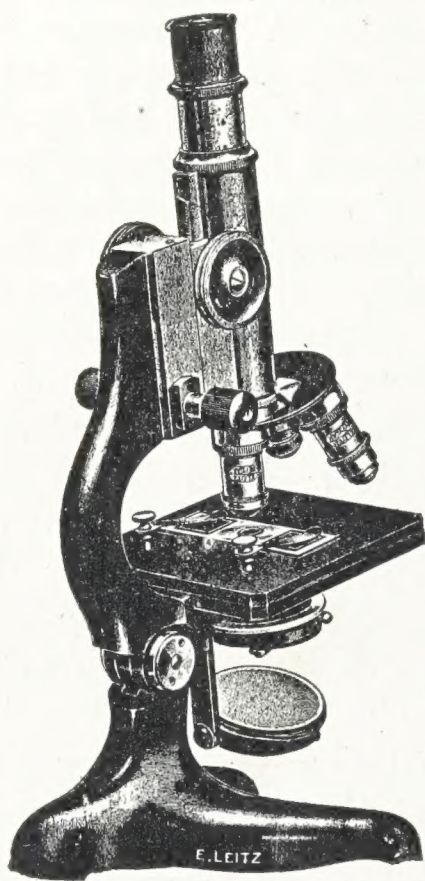
But when the period of continental elevation set in and some forms had to adapt themselves to drouth and life on land, it was the ganoids who were able not only to develop accessory respiratory organs capable of breathing air, but also of modifying the brain and its membranes so as to facilitate its aeration in a reduced supply of oxygen. Of the several modifications of brain form which met the requirements of these adverse conditions, one in particular has proved susceptible of unlimited further differentiation.

The more diversified conditions of life on land appear to require far more complex centres of higher correlation than those possessed by any fish and these were met by the amphibions, the first land animals, by widely evaginated thin-walled cerebral hemispheres. The nutritive requirements of such tissue are readily satisfied by its superficial position in close apposition with the rich blood supply of the pia mater and with the cerebro-spinal fluid of the meningeal spaces. Moreover such thin sheets of correlation tissue allow numerous functionally distinct fields to be in free communication through systems of association fibres of unlimited complexity. There is ample room in the subcortical white matter for such association fibres. Hence such a structure allowed of great development of the more labile individually modified sorts of behaviour as manifested by capacity for rapid learning by individual experience and intelligence in general. There is no assignable limit to which such structural specialization can extend. So we may think there is no limit to the possible functional modifiability. It is possible, but maybe improbable, that a more highly organized brain than the present human one may be evolved.

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**THE TIME FACTOR IN CERTAIN EMERGENCY CONDITIONS
OF THE ABDOMEN**

By HERBERT E. CLUTTERBUCK,

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IN conversation not long ago with an old friend who is a member of the present final year in medicine, I made the remark that there were certain emergency conditions in the abdomen which every medical man should feel competent to handle should he be so situated that he was unable to summon the assistance of a surgeon in time. It goes without saying that some doctors will be so situated in practice that a surgeon's assistance or a hospital are not within easy reach.

This paper will be an attempt to deal with the few abdominal conditions which might arise and in which the time factor is of the greatest possible importance.

What are the chief conditions with which any medical man may meet and in which the time factor is so all-important? They are: 1. The possible results of abdominal traumatism from such accidents as crushes, blows, falls and penetrating wounds. 2. Acute obstruction of the bowel due to strangulations either outside or inside of the abdomen of which the chief are hernias, torsions and adhesive bands. The consequences of all these conditions thus briefly alluded to are without surgical relief a certainly fatal issue, and the certainty of that issue is in direct proportion to the immediateness of the surgical relief. In every one of the conditions, if one sees the cases early or indeed at any time, waiting to remove to a hospital or to summon a surgeon, if much time will be consumed in his arriving, is to condemn the patient to almost certain death.

The writer has a vivid recollection of a case many years ago of a strangulated hernia occurring in an old friend in a town where there were four doctors. The diagnosis of strangulated rupture was made on the day of the onset of pain and yet another whole day was permitted to go by while a surgeon was summoned from a nearby city to operate. Then he found a hopelessly gangrenous bowel and so serious a degree of toxic shock that the patient succumbed within a few days. Such a death was a tragedy and more—it was indefensible.

It cannot be too often emphasized or too frequently repeated that the likelihood of recovery in all the types of cases to which I am alluding is enormously reduced with every hour of time which elapses without relief. No man no matter how inexperienced he may be in surgery should fail to grasp this fact. Let it be said now and emphatically that the surgery of the traumatized abdomen is simpler than that of the pathological cavity and its simplicity is further made more certain the earlier the physician intervenes.

In abdominal injuries, from the viewpoint of diagnosis, it is unfortunately the case that the greatest damage may not reflect itself in any early symptoms which have the appearance of seriousness. Occasionally shock has, because of itself, to be combated. But the practitioner should be on the alert to come to a comparatively early decision, that what he is dealing with as far as symptoms which resemble shock are concerned, is not

alone, shock purely and simply, but is in part also due to a continuing concealed hemorrhage.

What chances are there for the spontaneous cessation of intra-abdominal bleeding? They are, I would say, very slight, because the conditions which might bring about the cessation of hemorrhage elsewhere are not operative in a large cavity like the abdomen so that bleeding may go on and frequently does from very small vessels. I have seen the abdomen full of blood from hemorrhage continuing from a tiny vessel in the edge of an intestinal rupture. If the hemorrhage is from a solid viscus, that is, the liver or spleen, the spontaneous cessation of hemorrhage is no more likely to occur. In abdominal bleeding the peritoneal space is great and there is no way of bringing pressure to bear upon the bleeding area. So that in a patient seen soon after injury, if the condition of shock does not show within a very few hours, and after the use of resuscitative measures a continuous and continuing improvement in the pulse rate both as regards rate and quality does not occur, it is sufficiently certain that the patient's condition is due to a proceeding hemorrhage, and that alone demands immediate intervention.

When we come to consider the frequent cases in which there is not serious bleeding but in which there has been rupture of hollow viscera, and when we realize the equal importance of operating in time, as we can do if we are called in time, to prevent a spreading peritonitis with all its disastrous consequences, we will realize that it is better to open an abdomen and find that perhaps at the best an occasional case where no such injury had been suffered, than that we should form an erroneous conclusion in the other direction.

It should be laid down as imperative that the signs for opening the traumatized abdomen if seen in time should not be the signs of peritonitis. It is the safest stand to take that in any doubtful case the indications are for an immediate operation. It is certainly true that during very early hours allowing that no serious hemorrhage is proceeding but that a rupture of intestine has occurred, that the patient's state may not suggest the serious potentialities of the injuries which he has likely suffered.

It is not an uncommon thing to find in a man who has suffered a gun shot wound of the abdomen causing many holes in his intestine, that during these first few hours his pulse may be normal, his color and appearance of the best and only a certain mild soreness on palpation of the abdominal regions over the intestine at that part or parts traumatized. When we get marked distension and generalized tenderness they are evidences of widespread infection.

How much time then have we got after a patient has suffered such abdominal injuries as we are dealing with. We know from laparotomies done upon numerous patients within a period of six, eight and ten hours after severe and numerous intestinal holings that the first result of the injury on the intestinal neuro-muscular mechanism is to inhibit the function of peristalsis, and in this way the soiling of the peritoneum by the extrusion of intestinal contents is delayed a considerable enough time, should the case be seen early, to enable one to operate and to close the perforations without any fear of spreading infection and without the institution of abdominal drainage. It would seem to be true that the less

severe the intestinal injury is, the shorter this inhibitive period is likely to be.

In the course of say eight or ten hours from the reception of the injury, the intestine gradually shows evidence of recovery from its temporary functional inhibition until by the end of the first 18 or 20 hours its recovery is fully re-established, at which time and as a natural consequence the abdomen is a mass of peritoneal infection and any hope of successful surgical succor is almost negligible. If it is within our power then, we should never wait until the abdomen has become rigid, the distension marked, the pulse rate increased and increasing and the vomiting persistent, for if the doctor swithers, as the Scots say, and delays intervention until such symptoms are present, he has delayed too long.

In regard to obstruction of the bowel—very much the same remarks could be made as far as regards the urgency of early intervention. The doctor has here frequently the cause of the obstruction, such as an irreducible hernia, plainly in view. If it is an internal hernia or a torsion, the cause while not so plain gives rise to the same symptoms. These symptoms are usually violent, usually sudden in onset and both their violence and their suddenness may be considered as a measure of the completeness of the obstruction. Seen early—there is the severe pain, there is the state of shock always the consequence of intense pain, there is the nausea soon to change to vomiting—urgent and frequent—and added to these early symptoms there is the other capital sign, complete faecal stoppage, that is, neither faeces nor flatus are passed by the bowel.

Let us cite one brief but illustrative fatal case, where the cause was a volvulus of the sigmoid: A strong healthy young farm labourer was suddenly attacked some hours after his evening meal with a violent pain in his abdomen, a sort of intense colic accompanied with cold sweats, nausea and pallor. Soon he began to vomit and throughout the whole night the vomiting, the pains and the abdominal colic continued. On the evening of the second day he seemed a little easier but the abdomen was now considerably distended, the bowels had not moved nor had flatus been passed since the day before. During the night the situation altered seriously for the worse; next morning the pinched face, wretched pulse and coldness of the extremities, the faecal vomiting, the distension of the abdomen and the persisting and absolute constipation allowed no misconception as to the fast approaching termination.

Given such a group of symptoms with in addition the fact, striking usually even to the sympathizing friends, that the patient though plied with various things to take by mouth vomits everything which he does take, makes a picture of surgical emergency which should not require any further confirmation to point to the necessity for the earliest possible intervention.

The student should, firstly, divest his mind of the idea that he requires any complicated outfit of instruments. In all surgery the simpler the tools the better. He should have two pair of simple, straight intestinal holding clamps, and for the rest, the ordinary instruments which he would be certain to have are sufficient. If he has not got the clamps the bowel can be held and soiling prevented by two pieces of narrow bandage slipped through a hole in the mesentery and tied gently around the intestine.

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What are the surgical procedures which he may be called upon then to perform, to meet the conditions which may be present in such acutely emergent abdomens? They are:—1. The opening and closing of the abdomen. 2. The repair of holes in hollow viscera to which must be added the occasional necessity of doing an intestinal resection. 3. Measures for the control of hemorrhage from solid viscera either by suture or by packing, or occasionally as in splenic injury, by its removal.

One should open the abdomen to deal with traumatic cases, in the midline—and here let me urge the importance of making the incision adequately long. More damage is done by attempting to examine the abdomen through a small incision than was ever compensated by the smaller incision itself. Professor Rutherford Morris, of Newcastle, having this very thing in mind, used to teach his students that the long abdominal incision was not in itself any serious challenge to the future integrity of the abdominal wall.

Every man in operating in such cases should bear in mind that he may have to search the whole abdomen in order to be sure that he is not overlooking serious hollow visceral damage. To that end it is important that he adopt a definite plan of action and systematically follow it out. Such a plan is to find quickly some easily accessible portion of the intestinal canal—for instance, the caecum and terminal ileum—and then carefully but rapidly run through his fingers the whole of the small intestine to its jejunal flexure, or ligament of Fritz.

The writer not long since assisted at an operation on a boy who was struck by a motor. There was no external evidence of injury on the abdominal wall and yet on searching the small intestine—deliberately throughout, which as I have said, is so important—a rent over two inches long was found at the duodenojejunal flexure.

It is a good plan in a case in which multiple injuries are expected, to search the whole of the small intestine and to mark the injuries as they are found by a sponge lightly clamped over the damaged part and then doing all the repair together, when one knows the extent of the injuries.

Holes of the colon are suggested to the operator as soon as the abdomen is opened by the characteristic odor, a symptom which we know is not present in holes of the small bowel.

Now as to a method of repair: Here again the student may divest his mind of the idea that the repair of intestinal holes is a complicated proceeding or that the stitching methods are difficult to understand. Leaving out the very tiniest holes, which may be safely repaired by the simple application of a purse string suture—the essentials necessary in order that a wound of the bowel may be effectually closed against hemorrhage and leakage, are firstly, a stitch which co-opts all the layers of the intestinal thickness; and, secondly, upon this again should be superimposed a continuous Lembert suture. It is not of paramount importance what kind of suturing material one uses—thoroughly sterilized cotton or linen thread would do in emergency and cat-gut of course when it is available would be favoured by many.

In doing intestinal resection the same principles of suturing are employed. The damaged segment of bowel is held a short distance from the line of proposed sectioning, by the holding clamps. If a small section

only is being removed it may only be necessary to sever the mesentery at the bowel margin. If a large piece has to be removed it is better in order to save redundancy, to excise a wedge-shaped piece of the mesentery along with the damaged bowel segment. The bowel is now cut away by an oblique section which removes the greater amount on the convex side, the mesentery being clamped and cut until severed completely. The first layer of sutures, as I have said, is a continuous through and through stitch piercing all the coats, taking particular care with the mesenteric angle. These stitches should be not more than one-sixth of an inch apart, for it must be remembered that they not alone prevent leakage but represent the line of protection against hemorrhage when the holding clamps have been removed which they are when this first circle of through and through suturing is finished. The anastomosis is completed exactly as in the case of the repair of a hole by a superimposed circle of continuous Lembert stitching which includes the sero-musculature only and brings about a safely wide approximation of the surfaces of peritoneum. It is astonishing how quickly these surfaces become covered with lymph, so much so that in autopsies upon patients dying from other causes within three or four days after such types of intestinal repair, it is difficult almost to find the site of such intestinal suturing.

In such cases where the operation is done early and before the re-establishment of peristaltic function, beyond the careful removal from the abdomen of blood clot when present, drainage, generally speaking, is not necessary.

The suturing of the abdominal incision if the patient's condition justifies it, is of course best done in layers; but a through and through suturing with silk worm gut is of course more rapid and may be depended upon if introduced with care, to give a sound abdominal scar.

There remains to be said something with regard to the operation for intestinal obstruction. When it is due to external hernia no delay should be allowed. The advance to a thoroughly devitalized bowel will enormously increase with every minute following the strangulation. One exposes the hernial sac by means of classically placed incisions, and on opening the sac under such conditions it is usual to find some blood-stained fluid which acts as a protection to the imprisoned intestine from injury by the knife or scissors. Having opened the sac he should then gently and to a sufficient degree incise the constriction at the neck so that he may with ease draw out more of the intestine in order to submit it to proper examination.

It may be emphasized now that the signs given in works on surgery as to the viability of intestine so damaged may be relied upon. A knuckle of intestine blackened but with no loss of its peritoneal lustre, and in which on gentle douching with warm saline there can be noticed evidences, even though slight, of change of color, may be returned within the abdomen with confidence. If there is any question, of all the signs enumerated, the one it seems to me that is at once most striking and entirely dependable, is the normality of the peritoneal gloss. I have never had reason to regret the return of such a segment of intestine within the abdomen.

What are we to do when the involved segment is obviously hopelessly damaged? The answer is that it depends upon the condition of

the patient. If for any reason the operation is a late operation and the patient's condition is very bad, it is better to fix the intestine in the wall, pack it around with a little gauze and deliberately create a temporary intestinal fistula. But if the patient's condition is such that a reasonable prolongation of the operation is likely to be well borne, the damaged segment of intestine should be resected in the same way as described in the section of this paper referring to traumatism—with this difference, that the operator in intestinal obstruction must be very careful to go well beyond any possible evidence of intestinal change. That is to say, he must without any suggestion of doubt do his resection through as normal bowel as he can find, no matter how wide he may have to go. If he finds it difficult to do this through the comparatively small opening of his hernial neck, it might be better and safer to do his resection operation through a separate abdominal incision.

In a case of obstruction due to causes within the abdomen, such as twists and torsions, adhesive bands, etc., he will of course on opening the abdomen adequately, generally be guided to the site of the trouble by the distension of the intestine above the obstruction. The distension is very great, and it may be necessary and is often advisable to tap the involved loops with a trochar, thus getting rid of gas, thereby permitting collapse of the distended loops and greater ease in exploration, as well as in the treatment of the constricting cause. Adhesions may have to be snipped, twists untwisted, an intussusception expressed and occasionally a faecal fistula established as a life saving measure to be closed later after transfer to some central hospital.

The only case in which the writer ever had to do a resection of intestine for acutely obstructed bowel was in a woman who had a strangulated loop of small bowel tightly caught through a loop of an adhesion between the intestine and the top of the broad ligament upon which there had been an operation a year and a half previously—but it will not be out of place to again emphasize that resection of intestine in acute obstruction of the bowels would rarely be necessary if all cases were seen early and surgical relief immediately given.

No mention is made in this paper of those acute abdominal conditions which though they are of an emergency character are not, if we might with safety speak of the matter in degrees, quite so emergent as those which have been mentioned.

In the practice of medicine one is not infrequently faced with emergency situations which of course vary widely as to cause. In meeting them the greatest infirmity the practitioner can suffer from because of its effect upon the time factor, is the Infirmity of Indecision.

ON SOME PRINCIPLES ON THE EMPLOYMENT OF VACCINES

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THE progress of vaccine therapy and prophylactic inoculation is a story of the development of principles upon which our present practice is founded. The doctrine of protection by inoculation was inherent in Jennerian vaccination. By inducing a mild form of disease an individual could be protected from small-pox. The wider significance of the doctrine was first realized by Pasteur. When he found that an animal developed immunity following inoculation with attenuated bacterial cultures he realized that he was dealing with a general principle capable of wide application. Upon this principle he developed a vaccine against anthrax, and its use in sheep and cattle saved the agriculturalists of France many millions of francs. Later he developed a vaccine for rabies and in doing so enlarged his conception of the sphere in which protective inoculation might operate. The anthrax vaccine was given to protect healthy animals from possible infection. The treatment for rabies was not commenced until the patient had been infected, but rabies has a protracted incubation period and it proved feasible to immunize a patient more rapidly than the infection developed. Thus the sphere of inoculation was widened to include diseases in which the incubation period was sufficiently long to allow time for the development of immunity. In all his work Pasteur believed that immunity developed by inoculation was specific, and that living but attenuated organisms were necessary to establish it. At the close of his career he had formulated the great fundamental principles of inoculation.

Since Pasteur's time the scope and practice of inoculation have continually enlarged. Vaccines have been applied to the treatment of established infections. Numerous types of vaccines have appeared and various methods of administration have been advocated. But along with the apparent advance there have arisen unsolved and vexing problems. Uncertainties exist as to the indications for vaccine therapy, the dosage one should adopt, the respective merits of various types of vaccines, the relative value of an autogenous vaccine and one made from a stock culture, the development of non-specific immunity, the possibility of determining the effect of vaccines by measuring immunity responses; and upon these questions there is yet no final pronouncement. A certain amount of clinical evidence has accumulated and one sometimes finds clinicians who hold their opinions with great conviction. The majority, however, are not dogmatic, they are content for the moment to employ vaccines without a full explanation of success or failure and to look for further elucidation of the principles of inoculation by which they may guide their practice. It is with a brief discussion of these principles that this paper is concerned.

As a preliminary it may be useful to recall that any benefit derived from inoculation is referable to improvement in the level of immunity, and that "immunity" as used in this sense can be resolved by analysis into three factors—bacteria destroying power of leucocytes, antibody

content of blood, and resistance of fixed tissue cells. So far it has not been possible to obtain a complete picture of all the reactions involved in immunity. The analysis of the results of inoculation have been limited to certain factors which can be studied by the technical methods at our disposal. Since one cannot measure the whole mechanism of response to inoculation the question arises as to what extent reliable or useful information may be obtained through measuring one or more factors of this mechanism. For a discussion of the question the reader is referred to Sir Almroth Wright's book, *Studies on Immunization*, page 331. It will serve the purpose of this paper to quote the final passage: "You will now realize that the principle upon which as a foundation vaccine-therapy has been built up, is the principle that we should guide ourselves by evaluating in an accurate manner some one selected bacteriotropic element of which we have grounds to believe that its increase in the blood will prove to be correlated with clinical improvement".

Consideration of the principle just quoted forms a starting-point for a discussion of several questions which are suggested by it. What are the elements of resistance whose measurement has assisted the study of inoculation? What has been the basis of their selection? What are the inherent merits or limitations of the various elements for the purpose of studying inoculation? To what extent have such studies enhanced our knowledge, and evolved principles upon which practice may be based? With these questions in mind it is proposed to review the various methods that have been employed to evaluate the results of inoculation and to point out conclusions which may serve as working principles.

The Method of Clinical Observation

Clinical observation alone is sufficient to convince anyone—if that were necessary—of the value of inoculation. The alleviation of rabies, the prevention of typhoid fever are facts beyond question. In the United States Army in 1908, the last year before inoculation was commenced in that army, the incidence of typhoid fever was 320 cases per 100,000. In 1912, the first year in which all the troops were inoculated, the figure became 31 per 100,000, and in 1913 it was 4.4 per 100,000. Under campaigning conditions the differences would have been even greater. Massive clinical statistics have served a useful purpose. They are the only means at our disposal by which the value of inoculation may be judged in infections where the virus is still unknown. They have confirmed the value of preventive inoculation and have produced evidence in favour of non-specific immunity. Statistics have been an aid to other methods.

Clinical observation, as applied to individual cases, may leave no doubt in the mind of the physician as to the value of vaccine in certain instances, and information of value may be obtained in this way if the observer is cautious in drawing conclusions and is not misled by unwarranted enthusiasm. As a method it will not explain the reason for good results in one case and failure in another. In general one must conclude that neither massive statistics nor clinical observation of individual patients will carry us very far toward a solution of the fundamental problems of inoculation.

MEDICAL JOURNAL

Methods Relating to Leucocytes and Phagocytosis

In order to present clearly the important influence which a study of leucocytes and phagocytosis has had in formulating principles of inoculation it will be necessary to state briefly the mechanism of their activity and to point out to what extent a technique has been devised for measuring it. That these factors have occupied an important place is not surprising when one reflects that infections due to *staphylococcus* and *streptococcus* are chiefly combatted by means of leucocytes and that where *pneumococcus*, *meningococcus*, *gonococcus*, *B. anthracis*, *B. tuberculosis* and other bacteria are concerned, the activity of leucocytes plays an important rôle.

Bacterial destruction by leucocytes may be intracellular or extracellular. Intracellular destruction is accomplished, presumably, by digestive enzymes and requires as a preliminary the ingestion or phagocytosis of the bacteria. Extracellular destruction operates independently through bactericidal substances excreted by leucocytes. Although each of these processes merits a separate discussion it should be understood that they proceed concurrently, one supplementing the other and each playing a part in the mechanism of destruction.

The ingestion of bacteria is an inherent function of the leucocyte but cannot be completed by the cell alone. The presence of plasma or serum, is essential. Washed leucocytes deprived of serum will take up very few bacteria, so few that the number would be negligible as a factor in immunity. Phagocytosis therefore is a combination of two factors, the inherent power of the leucocyte to ingest, and the opsonic value of the serum. Each may vary independently and variations in either will affect the phagocytic function.

The opsonic value of the serum may be estimated by determining the opsonic index, the technique for which need not be discussed here. It is a measure of only one factor in phagocytosis. A more accurate evaluation of phagocytosis would take into account not only opsonin but the function of leucocytes as well. A technique for this has been devised in Sir Almroth Wright's laboratory by modifying slightly the technique of the opsonic index. If an individual A is under consideration and B is a normal, the following mixtures would be made:—

A leucocytes + A serum + bacteria

B leucocytes + B serum + bacteria.

By comparing the first mixture with the second, one arrives at a figure termed the phagocytic index. It was devised some years later than the opsonic index, and for this reason has not been used so extensively as the latter for studying inoculation, but undoubtedly it gives a more accurate indication of the level of the phagocytic function.

Phagocytosis, however, is but the first step towards intracellular destruction. It does not follow that all ingested bacteria are destroyed. Their fate depends upon the activity of the destructive mechanism, and here again we find serum and leucocytes working together. Just as opsonin aids phagocytosis so there is a quality of serum that acts on bacteria to render them more susceptible to intracellular digestion. This property has been termed the protryptic power of serum. Thus in intracellular destruction there are two factors to consider—the inherent intracellular capacity of the leucocytes to digest, and the protryptic

value of the serum. It is probable that each may vary independently. Direct measurement of this function has so far eluded the ingenuity of the technician but recent developments in technique have succeeded in demonstrating variations by indirect methods, as will be discussed below.

The extracellular destruction of bacteria through the agency of bactericidal substances excreted from leucocytes has been demonstrated experimentally. When leucocytes are stimulated by living or possibly by dead bacteria they may respond in this way. It is likely, too, that other chemical or physical stimuli may suffice; and it seems probable that the ability of the leucocyte to respond is a function that may be depressed or exalted. In this connection measurements can be made of the bactericidal power of the serum, in other words one can measure the response after it has occurred.

This discussion would not be complete without reference to a further technical development from Wright's laboratory, which gives a result based upon the collective action of leucocytes and blood fluids in destroying bacteria. It is applicable to any organism that will grow in blood in colonies which permit of counting. The method is to inoculate a known volume of defibrinated blood with a known number of organisms, for example, with *staphylococcus*. The inoculated blood is placed in a shallow chamber between two glass slides held apart with strips of vaselined paper. The open edges are sealed with paraffine and incubation is carried out. After twenty-four hours the colonies can be counted with ease. The number may be expressed as a fraction of the number of organisms inoculated or as a comparison with the number of colonies in another sample of blood used as a base line. During incubation in "slide-cells", as these chambers have been termed, all the agents of defibrinated blood which destroy bacteria have an opportunity to act. It is true that the blood is under experimental conditions which do not reproduce conditions *in vivo*, but nevertheless the method has furnished important information with regard to the effects of inoculation.

Having discussed the technical methods, what are the principles which each in turn has produced?

The opsonic index has been used extensively by many investigators and in spite of the fact that it takes account of opsonic variations only, it has thrown some light on the reaction following inoculation. In numerous cases, particularly in those infections where resistance is for the most part the work of leucocytes, a parallelism has been observed between the level of the opsonic index and the clinical condition of the patient. A rise in the opsonic index is a beneficial reaction, a depression may be considered harmful. Thus the level of the opsonic index has been employed as an indicator to follow changes in immunity after inoculation.

Experiments on this basis have helped to establish the principle of the negative phase, a term used to denote an early depression in the level of the opsonic index after the injection of vaccine. Even after beneficial inoculations this depression may be seen. It is transitory and precedes the rise which denotes improvement. It is, however, considered to indicate a period of decreased resistance, harmful while it lasts. A similar negative phase has been observed in the level of anti-

toxin after injection of diphtheria and tetanus toxin. It has been noted after the injection of ox blood into rabbits and after inoculation with rennet. After inoculation with typhoid vaccine the bactericidal power of the serum passes through a similar depression. The negative phase therefore appears to be a general phenomenon following inoculation. The duration and extent of the depression are related to the dosage of the inoculation; the larger the dose the more severe and prolonged the depression. To what extent this should influence the dosage and spacing of inoculation is a matter of opinion. Wright says: "Let it be observed that the risk of a negative phase comes seriously into consideration only when successive doses of vaccine are employed, and when the prophylactic inoculations are undertaken in the actual presence of infection". It seems probable that the danger of causing a serious depression of immunity through establishing a negative phase is in actual practice not very great. For the treatment of disease there should be no danger from this source if doses are employed which do not cause severe local reactions and if the intervals between injections are at least three days.

It has been stated already that in many cases a parallelism can be drawn between a rise in opsonic index and clinical improvement. On the other hand there are notable exceptions in which they do not coincide. When opsonic variation happens to be the chief factor concerned then the opsonic index will give a valuable criterion of changes in immunity level, but it is not surprising that discrepancies occur when one keeps in mind the other factors involved in bacterial destruction by leucocytes.

The phagocytic index has found a place in technical methods comparatively recently and therefore has not been employed so extensively as the opsonic index. It has, however, revealed the importance of the inherent function of the leucocyte to ingest. This is so important in phagocytosis that depressed leucocyte function will not be fully compensated by high opsonic value. Depression of this function accompanies bacterial toxæmia and there is evidence to show that in severe septicaemias the fundamental defect in the mechanism of resistance is a depression of the inherent function of leucocytes to ingest bacteria. Along with this one surmises a similar depression of the intracellular digestive capacity and the ability to excrete bactericidal substances. This is an important principle in the study and treatment of septicæmias.

Measurement of the bactericidal power of the serum in order to determine the excretory response of leucocytes is of value chiefly as an adjunct to other measurements. It is not in itself a criterion of the level of immunity but has a useful place in work on immunization. It may be pointed out here that normal serum has no bactericidal value for the *staphylococcus* and very little, if any, for the *streptococcus*. The bactericidal action of serum on organisms like *B. typhosus*, where it forms an important defensive agent, will be discussed in a separate section.

The method of the slide cell has furnished most important principles. The technique provides a result that includes the bacteria-destroying activity of all the factors we have discussed in this section, opsonin and phagocytic capacity of leucocytes, protryptic power of serum, intra-

cellular digestion, and extracellular bactericidal substances. Using this method it is easy to demonstrate a reduced killing power of the blood of a patient suffering from a severe infection. It is also possible to show an improvement after inoculation, and with this we are chiefly concerned at the moment. Slide cell results have made it quite clear that within four hours after the introduction of a suitable dose of vaccine subcutaneously, the blood attains an increased ability to destroy bacteria. This is a constant finding in normal individuals and it occurs also with infected patients if the infection is not too severe to prevent response. The practical importance of the reaction concerns the normals. The increase in killing value is nonspecific. It has been shown that inoculation of *B. typhosus* vaccine will increase the killing power of the blood toward *staphylococcus* to the same extent as inoculation of *staphylococcus* vaccine. Further, the increased killing power can be referred to improved intracellular destruction. Both the inherent digestive capacity of the cell and the protryptic value of the serum may be increased. The conclusion is arrived at indirectly. The increased killing in slide cells is not the result of change in phagocytic index nor of serum bactericidal value. The only other factor is the digestive function.

These findings have their application in transfusion. In cases of severe infection where the defensive mechanism of the patient cannot respond, transfusion may be employed with benefit. The introduction of normal blood, containing normal leucocytes is of value. But since one is able to increase the power of the donor's blood to destroy bacteria, since one can give to the patient a quantity of donor's leucocytes whose digestive function is greater than normal, it would seem advisable to inoculate the donor four hours before transfusion with a suitable dose of vaccine. This form of therapy is being used at St. Mary's Hospital, London, and has been given the name "immuno-transfusion". Experimentally it is sound. It remains for clinicians to pass judgment upon it after a careful study of cases in which it has been tried.

(To be concluded in the next issue.)

VISCERAL REFLEXES

R. P. MACKAY, '25.

THE work of a small group of men, notably Sir James Mackenzie, has drawn the attention of the medical world to the importance of early symptoms in the study of disease. The development of vast numbers of intricate instruments for the examination of patients has certainly given us a world of facts concerning disease, but they are facts, as Mackenzie points out,¹ which are as yet not correlated or fully understood, and which can be obtained only late in disease, after tissue destruction has taken place. The earlier a diagnosis is made, the more it comes to rest upon an analysis of subjective symptoms, such as aches and pains and functional disturbances. These symptoms are largely produced through the agency of visceral reflexes. By visceral reflexes we mean the production

of effects in various parts of the body by stimuli coming from the viscera, and acting through the autonomic nervous system. These reflexes are viscerosensory or visceromotor, depending on whether the effect is sensory or motor. The viscerosensory reflexes may be divided, for our purposes, into referred pain and referred tenderness, or hyperalgesia. By referred pain we mean pain which is caused by a pathological process in a certain tissue, but which seems to the patient to lie somewhere else in the body. For instance, heart disease may give pain along the ulnar border of the forearm. In the same way, by referred tenderness we mean hyperalgesia which lies in a tissue which is not the seat of the pathological process. In heart disease, for instance, the skin of the left forearm on its ulnar side may be exquisitely tender. Viscero-organic reflexes are those involved in such processes as emesis, increased pulse rate, vasomotor changes, etc.—activities involved in physiological processes. In addition, viscerotrophic reflexes have been described, but inasmuch as the existence of a trophic action of the nervous system is denied, we shall not consider them.

The anatomical basis for visceromotor and viscerorganic reflexes is well understood, and has been accurately mapped out.^{5 6} The cell bodies of the afferent neurons lie in the sensory cranio-spinal ganglia. Their fibres form synapses with connector neurons which lie in the gray matter of the cord or brain stem, and these connector neurons in turn form synapses with effector neurons which act on the viscera again. The afferent neurons also make synapses with cells which ultimately stimulate, through motor neurons, the extrinsic muscles of the body. Thus stimuli from the various viscera may pass into the spinal cord and back to the viscera, or out to the somatic muscles, or sweat glands, blood-vessels, etc.

But as yet we cannot be sure of the anatomical basis of the viscerosensory reflexes. The afferent autonomic cells in the sensory ganglia lie in close proximity to the cell bodies of the somatic afferent neurons. In addition, some of the somatic cell bodies are surrounded by a network of very fine nerve fibres, called the pericellular plexus, but whence these fibres come we do not know.⁵ It has been supposed by some that they come from visceral afferent neurons whose cell bodies lie in the autonomic ganglia, and that they carry stimuli from the viscera, but this is as yet only an hypothesis. However, if it is true, we have a mechanism for handing over autonomic impulses to the cerebro-spinal system, and thereby bringing these impulses into the field of consciousness. At any rate, it is certain that the autonomic nerves are intimately related to the somatic afferent nerves, and this relationship is undoubtedly the mechanism for the phenomena of viscerosensory reflexes.⁴

While referred pain and referred tenderness are very much alike clinically, the two must be explained on different grounds neurologically. In explaining referred pain, we presume an afferent impulse to arise in the viscera, to pass along an autonomic nerve to a dorsal ganglion, where it is handed over to a somatic afferent nerve and then conducted to the cerebral cortex by the usual tracts. This impulse seems to the subject to come from the area which is supplied by the somatic nerve which took the impulse over from the autonomic system. Thus, an impulse from an exhausted heart passes along a thoracic-automatic nerve to (let us say)

the II Thoracic ganglion. There it is handed over to a somatic afferent nerve coming from the ulnar side of the left arm. This impulse is then experienced as coming from the arm, because the subject has learned to associate impulses from the II Thoracic nerve with the arm.

To explain referred tenderness a different mechanism is necessary. For, given the referred pain in the forearm, as described above, why should touching the forearm cause pain? Such referred tenderness may even last after the disappearance of referred pain,¹ and under these conditions it is hard to understand why the area on the forearm should be hyperalgesic. Mackenzie¹ explains this phenomenon by saying that the continual bombardment of the II Thoracic ganglion cells with painful impulses from the heart puts it into a hyper-irritable state, so that ordinary sensory impulses from the arm now excite pain as well as touch. This explanation, based on a supposed hyper-irritability of the ganglion cells, admirably accounts for all the phenomena, but it must be considered only as an hypothesis. It is a very reasonable hypothesis, however, and very serviceable.

A great deal of work has been done to establish just what stimulus is adequate to produce pain or tenderness from the viscera. It is well known that the alimentary tract (except the extreme upper and lower ends) as well as all the other viscera, are insensitive to touch, temperature, pinching, cutting, and the like.¹ Some men, notably Hurst (Hertz) contend that heat and cold are perceived directly from the oesophagus and stomach.³ This is very doubtful, however, except possibly for the upper oesophagus, in view of the fact that all the rest of the alimentary tract is insensitive, even to cautery. As a possible explanation of the results which Hurst obtained, we offer the thought that hot substances in the stomach or oesophagus would heat the surrounding structures, particularly the very sensitive layer of loose areolar tissue just outside the parietal peritoneum, for it has been shown that though the visceral and parietal peritoneum are insensitive, yet in close contact with the parietal layer, and just outside it, there is a sensitive layer of tissue, which is known to be supplied with cerebro-spinal nerves, and not autonomic.

Mackenzie holds that spasm of smooth muscle is the only adequate visceral stimulus for pain, and he bases his opinion on a wide experimental and surgical experience. Hurst, on the other hand, holds that stretching of smooth muscle, such as might be caused by distension of a hollow muscular viscus, gives visceral pain. He bases his opinion chiefly on experiments in which he distended various parts of the gastro-intestinal tract with water bags.³ In these experiments he produced a sense of discomfort and pain by rapid distension. However, inasmuch as distension of the intestine produces muscular spasm in the form of violent peristalsis, and since pain may be produced by smooth muscle spasm without stretching, as in pylorospasm, we are inclined to favor Mackenzie's idea. The important clinical fact, however, is that this pain is not felt as coming from the viscera, but is referred to some area on the surface of the body.

The adequate stimuli for viscerogenic reflexes are varied, and cannot be discussed here, since it would involve a consideration of a field of physiology at once vast and poorly known. For instance, we know

that salivation, and increased secretion of urine occurs in angina pectoris, we know that vomiting occurs in a great many conditions, such as early scarlet fever, and we know that blanching or flushing of the skin occurs in emotional states, all of which are viscerogenic reflexes; but what their adequate stimuli are, or how they occur, we do not yet know. But it seems that referred pain at least has smooth muscle spasm for its stimulus, as witness the pain in gastric ulcer and carcinoma, pylorospasm, intestinal obstruction, renal and gall-bladder colic and uterine labor pains.

Having obtained a picture of the mechanism and adequate stimuli of these visceral reflexes, let us choose cholelithiasis as an illustration, and see how the mechanism is applied clinically.

The liver and gall-bladder receive their thoracic-autonomic innervation from the V-IX Thoracic segments. In addition, the capsule of the liver receives fibres by way of the phrenic from the III-IV Cervical segments.² The V-IX Thoracic spinal segments receive somatic afferent nerves from an area between the fifth interspace and a line drawn from the ninth interspace obliquely downward to the bottom of the umbilical area. The III-IV Cervical receive somatic nerves from the top of the shoulder between the clavicle and the spine of the scapula, and slightly up on the neck.

With stones in the gall-bladder we may have no symptoms immediately referable to the gall-bladder until a stone passes into the cystic duct. But once the stone passes into the duct, violent peristaltic action is set up in the muscular coat. Afferent stimuli pass over the thoracic-autonomic and phrenic (provided the capsule of the liver be involved, or pulled upon) nerves. The impulses go to the V-IX Thoracic and III-IV Cervical cord segments, and the patient feels pain in the right hypochondrium and in the right shoulder. This pain is severe and paroxysmal, coming in waves, and ceases when the stone passes into the duodenum, or back into the gall-bladder. In addition, we see hyperalgesia in the right shoulder and hypochondrium. This tenderness is in both skin and muscles, and may be so acute that the patient cannot bear the pressure of bedclothes on the area affected. The upper right rectus, which receives motor innervation from the intercostal nerves V-XII, becomes spastic.

It is noted that the pain and hyperalgesia does not cover the areas supplied by the III-IV Cervical and V-IX Thoracic nerves. We judge from this that only certain somatic nerves entering these segments are closely related to the nerves from the viscera. Other viscera, such as the stomach, which are innervated by autonomic nerves from the same segments, give reflexes to different parts of these areas, and are presumably in touch with a different group of somatic nerves. The question of the variability of these referred pain areas arises. In other words, does reference from the gall-bladder always occur in the same place? It is a very important question, for unless the reference is constant, no diagnostic value can be placed on the symptoms. One gets the impression from seeing cases in the wards that reference is fairly constant, though not by any means absolutely so. Thus, diagnosis on symptoms alone between duodenal ulcer and gall-bladder disease is often difficult or impossible, though typically the referred phenomena are distinct. More investigation is necessary before this point can be quite cleared up.

THE UNIVERSITY OF TORONTO

It is evident that to understand these visceral reflexes a thorough knowledge of the innervation of the viscera by the autonomic system, and of the segmental innervation of the cutaneous and muscular structures of the body is necessary. In addition, much has been learned about the autonomic nervous system by studying the areas to which pain, tenderness and muscle rigidity are referred. The future holds out tempting rewards to the man who studies visceral reflexes, and grievous penalties to him who will not do so. The material for study is fortunately ample, and accessible to every medical man, for scarcely a disease exists which does not manifest itself in early symptoms produced by these mechanisms.

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JOHN HUNTER—THE NATURALIST 1728-1793

HIS HUMANITY

By A GRADUATE.

THE modern boy collects stamps, more rarely coins; later, books or pictures. John Hunter collected "everything" dealing with natural history. At his death his museum contained 10,000 specimens.

John, the youngest of ten children, was born at "Long Calderwood" near Glasgow, in 1728. Like "the baby" in most families, he was not subjected to the stern discipline that is accorded to one and all in the typical Scottish home. His father was 70 years of age when John was born, and died 10 years later, leaving the burden of a large family to the mother. "Jackie"—the Benjamin of the family—disliked school and books. In after years he wrote, "they wanted to make an old woman of me—that I should stuff Latin and Greek." He wanted to get his education in the more natural way—by rambling amongst the woods, hunting for birds' nests, comparing their number, size, etc. The natural world was his university. (Peter McArthur, of Ekfrid, tells us that a boy raised in the country receives the equivalent of a university education.) "I watched the ants, bees, birds, tadpoles, and caddis worm. I pestered people with questions about what nobody knew or cared anything about." At the age

MEDICAL JOURNAL

of 17 he could neither read nor write. This lack of "school" education was a great handicap to him in his work in London. His lectures were not popular because of his prosy presentation—he seldom raised his eyes from his notebook. He often took Tr. Opii before entering the lecture room to overcome his nervousness. He tried to make students think and such teachers are seldom appreciated.

On the other hand he had learned to make accurate observations and to draw logical deductions—two of the prime necessities in any research student.

Up to the age of 20 he was "an idle uneducated boy upon his mother's hands." The thrifty Scotch home had been able to educate the two older brothers but John was "a great disgrace for a Scots boy living within walking distance of Glasgow College." The turning point came when he visited his elder brother William who had established a reputation in London as an anatomist. John was immediately set to work in the dissecting room. He worked hard and long so that within a year he was placed in charge of the dissecting room.

His health was precarious following an attack of pneumonia and he signed up for two years as a naval surgeon. Returning to London, he started in practice as a surgeon. His hobby came first—"collecting," very much as golf is said to replace business. He was wont to say, "I must go and earn the d— guinea," because he needed the money to buy more specimens for his museum.

Domestic Life

He was engaged to Miss Ann Home for seven long years but could not afford to get married. Finally the proceeds from the sale of one of his books improved his "financial circulation" and they were married. They seem to have been very happy but one unconsciously sympathizes with Mrs. Hunter. The home at Earl's Court was a veritable Zoo, where he kept animals for study ranging in size from a bee to a tiger. Mrs. Hunter must have had her problems in managing a home where "the first floor and back apartments were filling apace in so much he was not able to find room for Gamela Perda, the tallest animal known." "He cut off its legs and fixed it in the front hall.

John was "short in the grain" and an expert at swearing—a common custom in those days and which is still not unknown. One night he came home and found the drawing room filled with Mrs. Hunter's friends. "I have come home to study—I hope the company will retire"—which they all promptly did.

He studied the habits of the animals intimately—too intimately at times. A young bull, a present from the Queen, nearly killed him one day while he was wrestling with it. He was rescued by his servants. Another time a pet leopard escaped from its pen and was attempting to leap a fence—much to the consternation of the neighbors, but Hunter was able to persuade it by physical force to return to its quarters.

Hunter Museum

His museum with its many thousand specimens has found a home in the Royal College of Surgeons. The most expensive specimen in the col-

THE UNIVERSITY OF TORONTO

lection is that of the skeleton of the Irish Giant—costing 500 guineas, a small fortune in those days. John, as soon as he heard of the Giant's death in Ireland, sent his men to secure the body. Such had been surmised by the Giant who left a sum of money to provide for his burial at sea. The executors complied with the wishes of the dead man, but five hundred guineas made it possible for Hunter's friends to go along in the same boat with the executors and as soon as the body was cast overboard, Hunter's friends had no trouble in resurrecting it. In the background of Sir Josuha Reynolds' portrait of Hunter, the lower part of the skeleton can be seen.

Skin Specialist

Hunter divided all skin diseases into three classes: 1, those that sulphur can cure; 2, those that mercury can cure; 3, and the largest group, those the devil himself cannot cure.

His Death

He had inoculated himself with syphilis in order to study its course in "an impersonal way." Arterial disease resulted, manifesting itself chiefly as angina pectoris. Anger aggravated his malady. "Any scoundrel," he said, "holds my life in his hands." One day at St. George's Hospital, a discussion developed into "a flat contradiction" and "being unable to restrain his feelings"—in other words, he was swearing mad—he walked into the next room, and dropped on a couch where he expired.

DIETETIC TREATMENT IN DIABETES MELLITUS*

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IF one surveys the history of the treatment of diabetes mellitus it becomes apparent that successful treatment, of certain patients at least, has been accomplished in seemingly diverse ways. It is now universally admitted that diet, and not drugs, is the mainstay of any successful treatment of this disease. At various times certain articles of food have been stated to have particularly beneficent properties in controlling the affection. These have had their vogue and have been followed by others for which in turn great things were claimed and denied. The points not generally recognized were—the total glucose content of these diets and the individual variations in the tolerance of different patients for these foodstuffs. Any foodstuff may be suitable for certain diabetics but this same substance may prove most harmful to others. For the less severe cases of diabetes mellitus dietetic control alone will effect a considerable improvement in their condition. For a certain proportion of cases no type of dietetic treatment is adequate in controlling the disease. For such patients, fortunately not a large proportion of the whole class, "Insulin"

*Owing to the numerous requests for this article it is now reprinted with acknowledgements to the "Canadian Medical Journal" and Dr. W. R. Campbell.

(an extract of pancreatic islet tissue) has been recently introduced into clinical use in conjunction with dietetic treatment. It may be said, however, that there is no case, whatever its severity may be, in which it will ever be advisable to use insulin without due attention to dietetic principles.

Diabetes is a disease in which the body is unable to efficiently metabolize carbohydrate. It has now been proven by the work of Banting* and others that this is due to insufficient insulin production by the pancreas. Insulin is apparently secreted into the blood stream by the Islands of Langerhans. A number of investigators, notably Opie⁷, Allen² and Conroy⁴, have called attention to the degenerative changes which occur in the islet tissue of the pancreas of severe diabetes. In partially depancreatized animals, Allen^{1 2} has demonstrated that functional and anatomical damage to the islet tissue results from overfeeding, thus indicating the necessity in treatment of keeping the work of the pancreas within the limits of its capacity. The severity of diabetes is in direct relation to the patient's tolerance for "total glucose." This may be determined by placing the patient on a known diet and estimating the amount of glucose excreted in the urine. In calculating the total glucose content of the diet it must be remembered that it consists of 58 per cent. of the protein and 10 per cent. of the fat (the glycerine) as well as the preformed carbohydrate. When the diet is excessive, clinical cases of diabetes show evidence of damage to the pancreas in the reduced tolerance for total glucose which results. Rest to the pancreas must mean a reduction in the total glucose to be metabolized by the pancreas and the object of treatment should be to accomplish this result by suitable dietetic measures with or without the artificial administration of insulin.

Methods of treatment of diabetes having as a basic principle the reduction in the work required of the pancreas have been introduced by Allen³ and Joslin⁵. Their methods of total dietary restriction and the use of fast days at intervals prolonged the lives of many severe diabetics, and the rest to the pancreas often resulted in an increased output of insulin, the internal secretion, and greater tolerance for total glucose. This permitted of a more liberal diet being used. Though in certain cases of diabetes these methods have served admirably, it is unfortunately true that in other cases the necessary restriction in diet was so severe as to lead to marked under-nutrition. Patients fed insufficiently are partly starved and the body protein and body fat are called upon to make up the minimal number of calories required to sustain life. The under-nourished, severe diabetic is quite unable to perform any useful work and is very subject to infections which may induce a further reduction in tolerance. In the most severe cases the "fasting" treatment actually defeats itself as the increased production of carbohydrate from body protein makes it impossible to get the patient aglycosuric. It would appear desirable to avoid these extreme degrees of under-nourishment and to furnish the diabetic with a diet sufficient to satisfy his normal caloric requirements. It is apparent that in such a diet the carbohydrate and protein must remain low in amount since each of these require insulin for their combustion. It has been shown by Marh, Newburgh and Holly⁶ that two-thirds of a gram of protein per kilogram of body weight is sufficient to

*For a bibliography of Insulin see Macleod, J. J. R.: *Insulin and Diabetes*, B.M.J., II, Nov., 1922.

THE UNIVERSITY OF TORONTO

maintain nitrogenous equilibrium provided the requirement for calories is otherwise met. The additional calories of the diet must be derived from fat but the complete combustion of this substance takes place only when sufficient carbohydrate is also being burned. When carbohydrate is markedly restricted from any cause, acetone bodies are produced from fat and in diabetics acidosis and coma may result. Woodyatt¹¹ has suggested that one molecule of fatty acid may be completely burned while one molecule of glucose is undergoing combustion. Further work by Wilder⁹ and Schafer⁸ appears to show that under certain conditions as much as two molecules may be burned with one molecule of glucose and no acetone bodies result. The relative efficiency of protein, carbohydrate and the glycerine of the fat in preventing acidosis has been well discussed by Schafer⁸. Plans for the dietetic treatment of diabetes based on the foregoing considerations have been suggested by Woodyatt¹² and by Wilder¹⁰;

Though in certain cases the ratio of fatty acid to total glucose may be markedly different, Woodyatt¹² believes that in the long run a 1:1 molecular ratio is the most satisfactory. Wilder¹⁰ has introduced a chart for calculating a diabetic diet on a basis of 1.7 molecules of fatty acid to 1 molecule of glucose in the food (ketogenic antiketogenic ratio 1.7:1). Both these methods have a definite value in the treatment of diabetes mellitus. Some experience with the 1:1 molecular ratio made it apparent that too high carbohydrate tolerance was required to make it suitable for the majority of diabetics though more palatable diets might be constructed with it. The disadvantage of the Wilder ratio is that a large percentage of patients do not need it, that the ratio of carbohydrate to fat is very low, the choice of foodstuffs is thereby restricted and patients soon become tired of the monotonous diet. Of course some patients are encountered who will become aglycosuric only when on such a diet as Wilder's, but for the average patient a somewhat less drastic restriction is desirable. Only those who have seen it will appreciate the great difference a few grams of carbohydrate makes to these patients.

While recognizing the usefulness of varying the ratio of fat and total glucose in the diet in certain cases from any arbitrary standard, it seemed desirable to follow a method which would, to some extent, avoid these difficulties. After trial, a molecular ratio of fatty acid to total glucose of 1.3 to 1 was adopted as being more generally suitable. The method to be described has been tried out during the past two years in the Toronto General Hospital. It has proved of particular service in connection with the insulin treatment of diabetes. It is now felt that such patients as are unable to remain aglycosuric and at normal blood sugar levels on this diet should be given insulin in suitable amount to accomplish this object.

The plan of procedure is to ascertain the normal basal caloric requirement for their age, height, weight and sex, and construct a diet with particular reference to the principles discussed above. The diet is calculated as follows:

- (1) The patient is weighed and his height measured.
- (2) From Du Bois' Table (Table I) the surface area of the patient is obtained, and this when multiplied by the 24 hr. basal requirement in calories for the patient's age and sex (Table II, Aub and Du Bois) gives the normal basal caloric requirement for a patient at rest.

MEDICAL JOURNAL

(3) If the weight is obtained in pounds, inspection of Table I gives the equivalent in kilograms directly, and this latter figure times two-thirds, gives the number of grams of protein required.

(4) The basal caloric requirement (M) divided by 30, minus $\frac{1}{3}$ the protein in grams or, more simply, $C = \frac{M-10P}{30}$ gives the number of grams of carbohydrate required.

(5) Fat sufficient to make up the calories required is supplied by the formula, $F = \frac{M}{10} - \frac{P}{2}$.

TABLE I
Surface Area Chart (Du Bois)

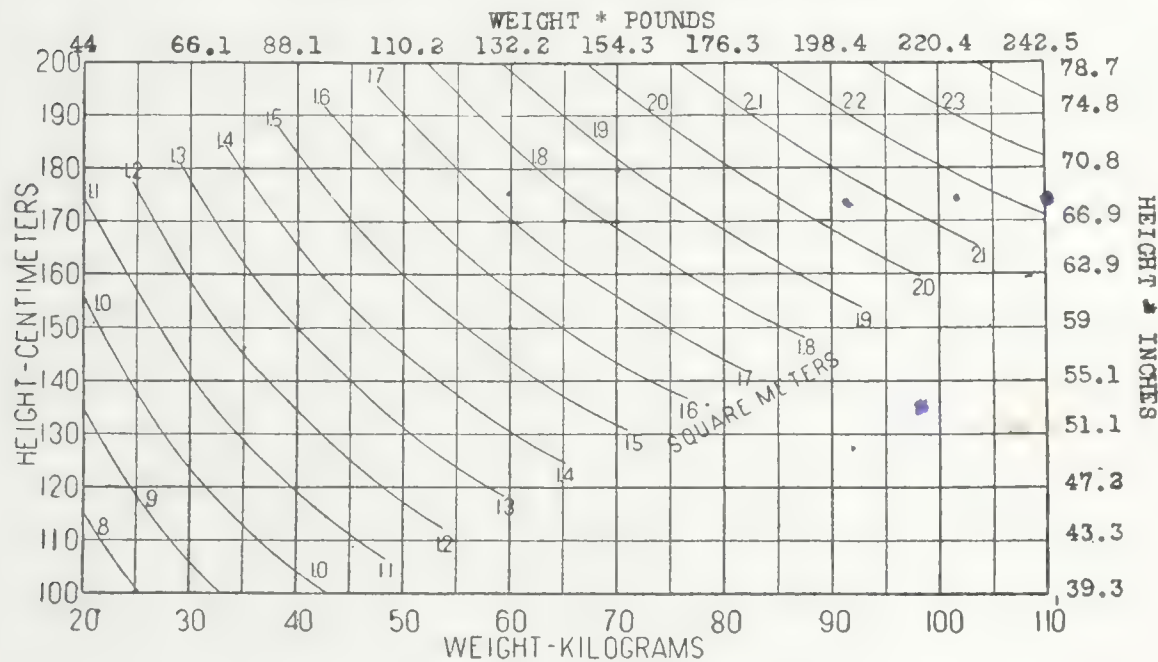


Chart for determining surface area in man in square metres.
Example: Weight 154.3 lb., Height 70.8 in. =1.88 sq. m.

TABLE II

Caloric Requirement per square metre of body surface (Aub-Du Bois)				
AGE	MALES		FEMALES	
	Cal. per		Cal. per	
Years	Hour	Day	Hour	Day
10-12	51.5	1236	50	1200
12-14	50	1200	46.5	1116
14-16	46	1104	43	1032
16-18	43	1032	40	960
18-20	41	984	38	912
20-30	39.5	948	37	888
30-40	39.5	948	36.5	876
40-50	38.5	924	36	864
50-60	37.5	900	35	840
60-70	36.5	876	34	816

Calculate requirement in children
according to weight. Up to
10 kg. 55 cal. per kg.
10-15 " 50 " " "
15-20 " 50 " " "

THE UNIVERSITY OF TORONTO

Example: A diet is to be constructed for a man of 55 years, height 5 ft. 7 in., weight 132 lbs. or 60 kgms.

Inspection of Table I shows a surface area of 1.7 sq. m. From Table II: $900 \times 1.7 = 1530$, the number of calories required per day (M).

The protein required $= 60 \times \frac{2}{3} = 40$ gms. per day.

The carbohydrate, $C = \frac{1530 - 400}{30} = 37.6$ gm.

Fat $= \frac{1530}{10} - \frac{40}{2} = 133$ gms.

With the composition of the diet in terms of the weight in grams of protein, fat and carbohydrate required it is a comparatively easy matter to construct a suitable diet from food tables.** On such a diet, provided he is kept at rest, the patient in the majority of cases will become sugar free, though this is not usually accomplished as rapidly as in the starvation method. Acetonuria is also controlled but somewhat more slowly than by Allen's method. The advantage of the method consists in the increased comfort of the patient and the fact that, subsequent to getting the patient aglycosuric by the Allen method, a considerable period is required to determine the patient's tolerance. On this account the total period of treatment is actually shorter than the starvation method.

While the patient is in bed or confined to his room a diet equivalent to his normal basal requirement is sufficient. With greater activity a larger diet is required. Before any such increase is advised it is well to estimate the fasting blood sugar. Values of 0.13% or over would seem to contraindicate such an increase, as patients with high blood sugar ultimately do badly. In most cases with a low blood sugar increase in the number of calories is the first object to be attained, and it is found that the addition of 5 gms. of carbohydrates and 20 gms. of fat, yielding 200 calories is a satisfactory method of increase as it provides a maximal number of calories without inducing ketosis. If this addition is well borne over a period of a week or more, a second and third increase in diet may be allowed, thus raising the food 600 calories above the basal requirement and restoring the patient to something like his old vigour. The ketogenic antiketogenic ratio of these additions to the diet is 1.7:1, somewhat higher than the original ketogenic antiketogenic ratio adopted for getting the patient sugar free but not higher than that based on Wilder's diet formula and quite safe so long as increases are small compared with the basal requirement.

Up to this time no additional protein has been used for three reasons: (1) it increases metabolism by its high specific dynamic action; (2) it is not as efficient an antiketogenic agent as carbohydrate; (3) the need for calories is greater. The diet at this point, though, is becoming somewhat top-heavy with fat and this means lack of variety in the menu. Variety can be provided by increasing the protein at this stage. It is thought that 8 gms. of protein has about the same power to cause hyperglycaemia as 5 gms. of carbohydrate, and consequently this amount of protein plus 10 gms. of fat is added to the diet. The ketogenic antiketogenic ratio is 1.7:1, calories, 122.

**Reference may be made to Atwater and Bryant—*Bull. 28, U.S. Dept. Agric., The Chemical Composition of American Food Materials*; Joslin—*The Treatment of Diabetes Mellitus*; Locke—*Food Values*; Friedenwald and Ruhrah—*Diet in Health and Disease*, etc.

MEDICAL JOURNAL

At this point a word of caution is worth while. The patient is now receiving 2,252 calories, or 722 calories (40-50%) above his basal requirement—sufficient for the performance of light work. It is the common experience that excessive work or excessive food intake ultimately results in reduction of the patient's tolerance for glucose and it is well to consider whether the increase in diet should not stop at this point. The activities of the patient do not require additional protein and it is believed that further increases in the diet should not be made unless the fasting blood sugar is normal.

The importance of maintaining low blood sugar levels in diabetes has been overestimated and was never so clearly demonstrated as now. At the present time there is a tendency even under insulin treatment to neglect this important factor in the belief that increased insulin will take care of any further loss of tolerance which may develop. Nothing could be more fallacious. The greater the severity of the case, the nearer it approaches complete diabetes, the greater the difficulty of properly regulating the dosage of insulin and the time of its administration, the greater the number of hypoglycaemic reactions encountered and the oftener the appearance of high blood sugar and glycosuria. In my experience and that of many others, it is unwise, considered from the standpoint of the ultimate result in treatment, to be satisfied with fasting blood sugar levels of more than 0.13%.

The applications of the principles of dietetic treatment discussed above may be illustrated by briefly reporting the following two cases:

Case I.—H. G., aet. 32, motorman. Admitted, October 16th, 1922; discharged, December 26th, 1922. Best weight, 156 lbs.; weight at onset, 145 lbs.; weight on admission, 119 lbs. Height, 5' 8 $\frac{3}{4}$ ". Surface area, 1.65 sq. m. Basal caloric requirement, 1,564 calories.

Present Illness.—On May 1st, 1922, complained of headache, dryness of the mouth, thirst and polyuria. On May 15th, sugar was found in the urine. He was placed on starvation treatment. He became sugar free; then was placed on a vegetable diet and gradually other foods were allowed. Has been losing weight, becoming progressively weaker and is now unable to become sugar free on starvation.

Past Illnesses.—Measles at 3 yrs.; whooping cough at 6 yrs.; trench fever, 1916-17.

Family History.—Negative for diabetes and obesity.

Examination.—Well-developed, poorly nourished, adult male. Skin and hair dry and harsh. Knee jerks absent and three carious teeth. Otherwise nothing abnormal found on physical examination. On admission he was excreting 50 gms. glucose and 10 gms. acetone bodies.

Treatment.—The patient was required to rest at first. Later the amount of exercise was gradually increased. He was placed on a diet of protein 35 gms., fat 139 gms., carbohydrate 40 gms., calories 1,551. During the first few days of treatment he excreted approximately 30 gms. of glucose and 5-11 gms. of acetone bodies. By October 25th, the sugar excretion had fallen to 5 gms. and the acetone bodies to 1.25 gms. October 30th, the sugar excreted was 1.7 gms., and acetone bodies, 3 gms. November 2nd, and continuously thereafter, he has been aglycosuric and the Rothera test has shown only the occasional trace of acetone bodies. The blood sugar levels showed gradual improvement—October 17th,

THE UNIVERSITY OF TORONTO

0.227%; 23rd, 0.174%; 27th, 0.190%; 31st, 0.137%; November 3rd, 0.157%; 7th, 0.120%; 14th, 0.130%; 18th, 0.156%; 21st, 0.118%; 24th, 0.143%; 28th, 0.124%. During this time he gained $7\frac{3}{4}$ lbs. in weight. After 44 days on the basal maintenance diet, the food intake was increased to protein 35 gms., fat 159 gms., carbohydrate 45 gms., calories 1,751. The blood sugar continued to remain low, being on December 1st, 0.105%; 6th, 0.110%; 7th, 0.120%; 14th, 0.095%. December 16th, 18 days later, a further addition of 200 calories was made to his diet, raising the intake to 1,951 calories. Two subsequent blood sugar tests showed values of 0.105% and 0.103% respectively, and the patient was discharged on December 26th, having gained $12\frac{3}{4}$ lbs. After the first few days in hospital the patient commenced to increase his activities and to ask for work to do. Before he left he declared that he was doing more work than was required of a motorman, and desiring more to do. Patient on March 19th weighed 141 lbs.; had been continuously aglycosuric and felt more than competent to do all the work required of him. His blood sugar was 0.112%. Were it not that he is increasing in weight on his present diet a further raise in diet might safely be allowed but in view of this fact it has been thought advisable to allow as much rest to the pancreas as possible.

Case II.—F. D. H., lawyer, age 52. Height, 5' 9". Weight on admission, 137 lbs.; best weight, 195 lbs. Surface area, 1.75 sq. m. Basal caloric requirement, 1,575 calories. Admitted to hospital, December 20th, 1922; discharged, February 12th, 1923.

Present Illness.—Became weak and polyuria developed three years ago. Glycosuria was discovered and he was placed on dietetic treatment. As improvement was not marked he went to a "sanitarium" for several months, where he lived on a semi-restricted diet. His general health improved; he felt stronger, put on weight and was sugar free in several morning specimens of urine tested. He probably was not completely aglycosuric throughout the day. After discharge, he gradually lost weight and became discouraged, despondent and "too weak to drag himself around", and reported for treatment.

Past illnesses.—Children's diseases.

Family history.—Negative for diabetes and obesity.

Physical examination.—Revealed no abnormalities except marked loss of weight and muscle tone.

Treatment.—On admission he showed a moderate degree of glycosuria without acetonuria. Blood sugar, 0.196%. He was placed on a basal diet of protein 41 gms., fat 138 gms., carbohydrates 38 gms., calories 1,572. He became sugar free at once, and the blood sugar fell to 0.129%. On January 3rd, two weeks after admission, the blood sugar was 0.116%, and 200 calories were added to the diet in the form of 5 gms. of carbohydrates and 20 gms. of fat. January 13th, the patient had been continuously aglycosuric and the blood sugar was still 0.117%. 10 gms. of carbohydrates and 8 gms. of protein were given to assist in stopping the slight acetonuria which developed. This proved effective. The patient remained sugar free, but the blood sugar rose slightly to 0.122%. In spite of this the diet was raised on January 27th to protein 49 gms., fat 200 gms., carbohydrates 65 gms., calories 2,256. The blood sugar rose to 0.140%. The ratio of ketogenic to antiketogenic substances in

MEDICAL JOURNAL

this diet is as 1.26:1, a safe level as is shown by only minimal traces of acetone bodies appearing in the urine occasionally. The diet remained the same and the fasting blood sugar level fell to 0.12% on the day of discharge. During the first eight days of treatment the patient lost 5 lbs., but regained this before discharge.

The mental change in this patient was quite remarkable. As he became stronger his despondency disappeared and he became interested in things apart from himself. Within a few days he was demanding more food for his increasing energies. On discharge he was getting a diet of 2,253 calories or 681 calories (43%) above his basal caloric requirement. This provided him with all the energy he required and, in fact, he regained his lost weight on it. He was discharged, feeling well and able to take long walks without fatigue.

DISCUSSION

These cases were selected from among a number of patients treated by this diet. The first case illustrates the comparatively slow response to dietetic treatment not uncommonly seen in these patients. Attention may be drawn to the plan of increasing the diet slowly as the period of relative rest to the pancreas is probably of value in promoting increase in tolerance for glucose. The second patient responded to dietetic treatment more rapidly because of a greater remaining tolerance for total glucose. The diet was increased comparatively slowly and he showed a satisfactory increase in his ability to utilize carbohydrate.

It should not be forgotten that the most satisfactory results are to be obtained when the food taken is digested and absorbed. As pointed out by Woodyatt¹² it is the metabolizing mixture of fats and glucose in the body tissues which determines the presence or absence of ketosis and this is borne out by clinical experience in the treatment of cases given improperly constructed diets in which marked disparity between the glucose and fatty acid obtained. With the damage to the islet tissue of the pancreas there may be, and in severe cases often is, damage to the acinar tissue with deficiency of the external secretion of the pancreas resulting in imperfect digestion of food-stuffs, and a totally different mixture being metabolized than is being fed. This possibility should not be lost sight of in the search for a cause of ketonuria in a case under treatment. In the more severe diabetics a morning ketonuria may be noted which disappears after 10-11 o'clock when the carbohydrate taken at breakfast is being metabolized. This ketonuria is never very serious but serves to remind us of the preferential utilization of carbohydrate over fat when both are available for energy production. It can sometimes be controlled by feeding a portion of the carbohydrate late in the evening. This procedure should be used with caution, however, since increase in the number of meals apparently increases the carbohydrate tolerance and one may be tempted to increase the patient's caloric intake in this way. Many devices such as, increased number of meals, small amounts of carbohydrate given an hour before the meals and active exercise after meals have been employed to increase the carbohydrate tolerance. The improvement is more apparent than real, and is but temporary in nature. They cause a stimulation of the

pancreas and more insulin is produced but the increased work injures the pancreas and ultimately lowers the tolerance of the patient for glucose.

When patients have passed through a period of undernutrition due to their disease or their previous treatment they very readily gain in weight when placed on a suitable diet. The diet here suggested is not actually the basal requirement of the patient but his calculated requirement under normal conditions. In reality, severe diabetics, free from acidosis and on diets low in protein so that the specific dynamic action is low, have basal metabolic rates of 70-90% of the normal; and this explains why patients placed upon such basal caloric diets actually gain in weight when they are relatively inactive. Within limits this increase in weight is desirable but it should not be forgotten that increased weight means increased caloric requirement and increased work for the pancreas. In the more severe cases it is felt that it is advisable to allow them to gain up to within 10-15% of the average weight for their height and age. This is within the normal variation and should provide a measure of protection against infection. The overweight diabetic is advised to reduce in weight as his tolerance will improve by so doing. This may be done by keeping him on a basal maintenance diet and gradually increasing the work he is doing, or by supplying protein and carbohydrate as per formula and limiting the fat. If this is done care must be taken to avoid over-fatigue and should evidence of acidosis develop it should receive prompt attention.

It is well known that diabetics are more subject to infections than other individuals, and these tend to run a more severe, more prolonged course than in other people. The toxic condition induced by the infection causes a loss of tolerance for carbohydrate which may be either temporary or permanent. Much may be done to combat the infection by placing the patient on a suitable diet. Adequate surgical treatment of infections often involves operation and this was formerly attended by a very high mortality in the diabetic. Dietetic treatment of these patients improves the operative risk. It is now felt, however, that most satisfactory results are obtained with an adequate diet containing considerable extra carbohydrate and sufficient insulin to maintain the patient aglycosuric with a normal blood sugar level. Local, spinal or gas oxygen anaesthesia are the preferable methods. Chloroform should never be used as there is grave danger of severe liver damage and coma resulting in diabetic patients unable to store glycogen.

Institutional treatment of diabetes has not received much attention in Canada, partly because of lack of adequate facilities and partly because of the apathetic attitude of some practitioners who vainly imagine that they can get just as good results under home treatment. In all cases it is advisable to institute treatment in a hospital where accurate examinations may be made, where food may be properly selected, cooked and served, where the patients may be trained in dietetics as applied to their disease, the measurement of food, the testing of the urine, etc. There is, of course, no necessity in most cases for a prolonged stay in hospital as a period of three weeks to a month is sufficient to get the patient properly started; he then may be treated as an ambulant case. The additional value to the patient repays the cost many times over and to the physician it often means the difference between satisfaction and disappointment in the treatment of the case.

MEDICAL JOURNAL

SUMMARY

The principles underlying the dietetic treatment of diabetes mellitus are discussed. These are equally applicable to the treatment of diabetics with insulin and it is emphasized that without attention to proper dietetic regimes insulin is capable of much harm. For the patient who can live on a properly balanced, adequate diet, insulin is available to protect him from emergencies arising in his disease. Types of diets are discussed and a simple method of calculating a standard diet for diabetics is suggested, together with its application in treatment.

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A CONSIDERATION OF SOME LIVER FUNCTION TESTS

(continued from last issue)

IVAN R. VAILE '24

CRISE *Hémoclasique* of Widal—It is known that the injection of a certain quantity of commercial peptone into the general circulation of a dog will promptly result in a crise hémoclasique. This syndrome is an evidence of the upset of the colloidal balance of the blood and is characterized clinically by leucopenia, a fall in blood pressure, hypercoagulability, and a change in the refractive index of the serum. Widal, Abrami and Iancovesco¹, in 1920, stated that a leucopenia following a standard protein meal is to be regarded as a delicate test for hepatic insufficiency. If after a heavy protein meal, samples of blood are taken from the general circulation as well as the portal vein, they will yield on chemical examination no trace of either a proteose or peptone. Widal by means of a biologic reaction was able to demonstrate the presence of these substances in the portal blood. For this purpose, he momentarily established an anastomosis between the portal vein and the inferior vena cava during the digestive period by a process similar to that used in making an Eck's fistula. Several minutes after the connection had been made, a typical crise hémoclasique resulted. This experiment was controlled by repeating the same test on unfed dogs. These studies show that the products of digestion which are normally absorbed into the portal vein can, when they gain entrance to the general circulation, cause a disturbance of the colloidal balance of the blood analogous to that resulting from the direct injection of commercial peptone.

On the basis of his investigations, Widal formulated the hypothesis that the peptones, proteoses, and other disintegrating protein substances

found in the portal vein during the digestive period, are arrested and transformed by the liver. This action he designated as the proteopexic function of the liver. It seemed probable, therefore, that the proteopexic function would be deficient in various hepatopathies, and that this defect would be associated with a crise hémoclasique, following ingestion of a protein meal.

Technique of the Test—(1) The subject to be examined abstains completely from food for a period of at least 5 hours preceding the test. The ingestion of nitrogenous food, no matter how small the amount, greatly interferes with the reaction.

(2) A leucocyte count is made and then the subject drinks 200 c.c. milk (a glass of milk, the exact amount not being essential).

(3) Subsequently the leucocytes are counted at intervals of twenty minutes for a period of two hours. Normally there is a slight leucocytosis following the ingestion of the milk and the count never falls below the pre-alimentary level. Recently, Feinblatt³ carried out this test on eighty healthy medical students and in every instance there was some degree of leucocytosis, and in no case was there a leucopenia. The occurrence of a post-alimentary leucopenia is considered pathologic and an evidence of hepatic disease. This leucopenia when present usually appears in the first hour. The other signs of the crise hémoclasique, viz., the fall in blood pressure, the increased coagulability of the blood, and the diminished refractive index of the serum, accompany the leucopenia. The leucopenia, however, is the most sensitive and the easiest to determine.

Theoretically, this test is attractive, but it has not stood the clinical test. Einhorn⁴ reports a number of cases of cancer of the liver and the patients died shortly afterwards. The liver in these cases was diseased to such an extent that the whole liver was cancerous, and the patients died within a short time; yet in those cases a normal response was obtained to a protein meal.

Laevulose Test—In 1910, Strauss⁵ introduced a test for liver efficiency which he based on the differences observed in the urine of normal and pathological cases following the oral administration of 100 grams of laevulose. In his series of cases with liver affections 90 per cent. showed laevulosuria, whereas only 10 per cent. of his normal control cases exhibited this when tested in a similar manner. In the majority of his positive cases the laevulosuria was observed at the end of the first hour. Churchman⁶, who further investigated this test, regarded it as helpful, but far from conclusive. He obtained positive results in a number of normal persons and failed to detect the presence of laevulose in the urine of definite cases of hepatic disease.

It has been shown by Hopkins⁷ and MacLean and de Wesselow⁸ that the administration of glucose causes a rise in the blood sugar values, a definite form of curve being observed. Following a dose of 50 gm. of glucose the blood sugar rises from the fasting level of about 0.1 per cent. and after reaching a value of 0.15 or 0.16 at the end of about an hour, rapidly declines and at the end of one and a half to two hours the original level is again reached. In 1913, Schirokauer⁹ carried out a series of experiments on the blood sugar content after the oral administration of laevulose, in normal persons and in those suffering from hepatic disorders. After

giving 100 gram. of laevulose he carried out a single blood sugar estimation one hour later. Instead of a value of about 0.15 or so being obtained, only the slightest rise in blood sugar was obtained. In subjects of liver disease the rise was marked, values up to 0.19 being observed. At the same time, laevulose was found in the urine in the majority of the cases, although this did not necessarily show a parallel with the rise in blood sugar values.

The laevulose test depends on the fact that laevulose is unable to cause a rise in the blood sugar value, such as takes place after the ingestion of glucose. Glucose is not assimilated and stored as quickly as laevulose. Even in a healthy person it increases in the general circulation as observed by following the blood sugar curve over a period of one to one and a half hours. Winter and Smith¹⁰ claim that the form in which it circulates is that of γ (gamma) glucose, and that the production of γ glucose is essential before assimilation can take place. Since fructose is probably more easily converted into this form than glucose it is reasonable to suppose that the conversion and subsequent storage of fructose takes place more rapidly than is the case with glucose. Consequently laevulose does not appear in the blood to the same extent as glucose immediately following its ingestion. If, however, a pathological condition of the liver exists, the enzyme or substance causing this conversion may be less active or so delayed in its action that the fructose instead of undergoing a rapid conversion into glycogen, as is usually the case, circulates in the blood and gives rise to the blood sugar curve observed in pathological conditions of the liver. Winter and Smith¹⁰ have been unable to confirm the presence of laevulose as such.

Technique of the Test—Test is carried out in the morning and no food should be taken for two and a half to three hours before the commencement of the test. Obtain a specimen of urine about 15 minutes before the test. Take a sample of blood before giving laevulose and then give the patient 50 grams of laevulose dissolved in 100 c.c. of cold water. Make blood sugar determinations half hourly for 1½ hours and longer if necessary.

In persons in whom no hepatic disease is present, the average rise is about 15 mg. The actual height of the curve rarely rises beyond .13 per cent. and appears largely dependent upon the blood sugar level at which the experiment commences. A fasting blood sugar value varying from .065 to .12 per cent. is to be regarded as within normal limits. Usually within 1½ hours the blood sugar curve has returned to the resting level. A blood sugar value of .12-.13 per cent. is not in itself evidence of a pathological condition. If, however, the height of the curve exceeds .135 per cent. and the actual rise in value from the original level exceeds 30 mg., a degree of liver inadequacy is presumed. The prolongation of the curve, a high blood sugar value persisting at the end of 1½ hours to 2 hours is strong evidence of such a disorder.

In a recent investigation, Tallerman¹¹ observed that the renal threshold for laevulose is far lower than that for glucose and that the majority of normal persons exhibited laevulosuria following a slight rise in the blood sugar curve and after the ingestion of a comparatively small amount of laevulose. The threshold varies in different individuals, but lies between

a blood sugar value of 0.115 and 0.13 per cent., as compared with values of 0.17 and 0.18 per cent. which is the normal renal threshold for glucose. It is on this account that Strauss's test is of little value. There is reason to believe that the purer the laevulose the flatter is the curve obtained.

Tallermann¹¹ also observed that the liver is in no way affected, as determined by the laevulose test in normal pregnancy. The renal threshold in this condition, however, is practically non-existent. Some evidence was obtained pointing to a disturbance of liver function in one out of two definite cases of eclampsia. In the other no change was apparent.

In catarrhal jaundice the laevulose test invariably indicates a disturbance of liver function, a fact tending to confirm the view that it is due to a toxic or inflammatory change in the liver cells and not to inflammatory obstruction of the bile ducts.

Conclusions—

(1) The crise Hémoclasique will bear further investigation. The majority are of the opinion that as a liver function test it is practically useless.

(2) The indications furnished by the laevulose test and by the phenol-tetrachlorophthalein test correspond and are reliable. Investigations with both tests have determined that the liver is intact in normal pregnancy. In the toxaemias of pregnancy the degree of liver damage as indicated by the tests is proportional to the toxic symptoms.

(3) The Van den Bergh reactions are useful to differentiate between obstructive and hemolytic jaundice and the indications furnished in acute cases are reliable. In chronic cases of jaundice the information is not as reliable as in the acute cases.

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SOME INHABITANTS OF MAN AND THEIR MIGRATIONS

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Reviewed by A. H. Walker, '29.

IT has been learned that sexually mature worms cannot usually reproduce a new generation of adults within their host. Each adult worm must have entered the body as a microscopic form. It has been found, also, that, with one exception, the eggs or or young of these parasites cannot immediately infect another

person after they have passed out of an infected person. A period of delay must intervene before the young forms attain sufficient maturity to become "infective." The changes which take place in the young parasite during this period are such that the resulting "infective stage" has no likeness to the newly born. Similarly it bears no resemblance to the adult which it will eventually form. Difficulty in recognizing the infective stage has been the main obstacle in the conquest of the parasites. By the introduction of zoological methods it has been made possible, in most cases, to recognize the infective stage, and so prevent the spread of the disease. It has been shown that each parasite has its own special method of approach and that this practically never varies. Further, it is found that parasites cannot proceed in their destined course unless special conditions prevail. In some species these factors of success are matters of temperature, and humidity. In others, the young worm must obtain, within a brief period, shelter and nutriment in some particular invertebrate or even vertebrate host, in which to undergo its essential metamorphosis.

In recent years various discoveries have been made regarding the migrations of the most important parasites of man.

One of the most important observations was made by Kuchenmeister, on the nature of the bladder worms which are found in organs of the body unconnected by natural passages with the outside. These parasites never develop genitalia, nor give rise to eggs. It was discovered that in each cyst there was always a bud bearing four suckers which greatly resembled the head of a normal tapeworm. Kuchenmeister found that a dog having eaten a cyst taken from the brain of a sheep, shortly began to suffer from tapeworms, and numerous tapeworm eggs appeared in its excrement. Some of the eggs were fed to sheep. The animals soon showed symptoms of "staggers" due to the pressure of growing cysts on the surface of the brain.

The same experimenter noted the marked similarity existing between the hooks borne by the bud of the cystic worms found in pork, and those on the head of the common tapeworm found in man. He administered some of these cysts to volunteers and later found them infected with the hooked tapeworm, *Taenia solium*. Pigs were then fed with eggs from the excrement of a person infected with *Taenia solium*. When killed, the flesh was found to be infested with typical cysts. As no adult tapeworm occurs in the intestine of the pig, it was evident that the development of the "dropsical" or "cystic" stage was a normal and not merely an aberrant phase, in the cycle of *Taenia solium*.

A hookless form of tapeworm is also a human parasite. Leuckart, having heard that this type of tapeworm was common among the natives of Abyssinia—who do not keep pigs, but rear cattle in large numbers—determined to feed a calf with eggs passed by a patient known to be infected with this hookless form. The calf, when killed later, was found to be infested with cystic worms, different from the cystic stage of the armed tapeworm. These experiments showed that certain parasitic worms require a second and different species of host in which to pass a portion of the life-cycle, and that each species has its own special intermediary host.

The importance of determining this intermediary host for each species

is illustrated in the migrations of the 'broad' tapeworm, a common parasite in countries bordering the Baltic. This species is practically unknown save where fresh water fish form an important item of diet. Braun, in 1881, found in the flesh of perch, pike and allied fish, a larvae stage, which when swallowed by volunteers, eventually developed into mature specimens of the "broad" tapeworm. Repeated experiments, however, failed to produce the developmental stages by submitting these species of fish to infection with the eggs of the adult parasite. In 1914, Janicke showed that a second intermediary is needed. After hatching from eggs, the tapeworm young are swallowed by a species of Cyclops. In the body of this minute crustacean, the so-called "water-flea," they undergo preliminary development. When the infected Cyclops is swallowed by a perch or pike, the parasite is set free and migrates to the muscles of the fish, and after further growth attains the infective stage, remaining in this situation until the fish is in turn eaten by a human being.

Nearly related to the tapeworms are the flukes or Trematoda. The best known example is the liver-fluke which infests sheep and cattle. In man, allied species of flukes inhabit the liver, the lungs, and the blood-vessels.

The knowledge of the migrations of *Fasciola hepatica* begins with observations made by Steenstrup. Several groups of asexual flukes had early been recognized. They were placed in isolated "genera" to which the names *Redia*, *Cercaria*, etc., were given. The so-called genus *Cercaria* comprised larval Trematod, which enjoy free locomotion in water and have a tail with which to propel themselves. Steenstrup showed that these free swimming "cercariae" in some instances attacked fresh water snails and in the tissues of these became "pupae". Within these cysts were found later young forms which seemed immature flukes. This linked the cercaria with the fluke, but it remained to link the cercaria with the egg. When Bojanus observed that cercaria swarmed out of "king's yellow worms," which occur in the interior of snails, and which possess the character of the so-called genus "*Redia*," the link was completed. The fluke parasites of man are *Bilharzia* worms, occurring in the blood; *Clonorchis sinensis*, occurring in the liver and associated ducts, and *Paragonimus ungeri*, occurring in the lungs.

In combating these parasites, it is first necessary to know by what means the cercaria of each species enters the human body, and in what phase in the development of the parasite outside the body can it be most easily destroyed.

Facts learned have shown that either the use of fresh water crabs and fish must be restricted and these animals only allowed as food after sterilization by heat, or some attempt must be made to eradicate the molluscan intermediary which is essential to the parasites' development.

The roundworms, or nematoda, form by far the greater proportion of the entozoa of man. The various species present different modes of migration. In some cases, development takes place within the egg shell, which after a necessary period of delay enters the body as an accidental contamination of food. The migrations of the Guinea-worm and Hook-worm are of special interest.

The adult Guinea-worm lives wholly in the connective tissues under

MEDICAL JOURNAL

the skin. When sexually mature it discharges a powerful irritant which causes the overlying skin to ulcerate. The worm protrudes through the ulcer and discharges a milky fluid which contains myriads of young. It was proved that the young Guinea-worms, living in water, entered and metamorphosed in the body in the bodies of cyclops. Leiper showed that on the completion of this metamorphosis the larvae become quiescent and remain encysted in the body cavity. When the infected cyclops are taken into the human body, the larvae, released by the gastric juice, make their way to the connective tissues, and after several months develop into almost full grown Guinea-worms.

The "ankylostome" or "hookworm" is an intestinal roundworm about half an inch in length. The "laziness" and general degeneracy of white people in tropical lands is due to the ravages of this parasite. The hookworm requires no intermediary host. The eggs hatch and metamorphosis takes place in moist soil. The larvae are able to penetrate the skin, and upon so doing enter the small veins and are carried to the heart. Thence they pass in the blood stream to the lungs, where they are stopped by the fine capillaries. The larvae then burst into the air sacs, and are carried by mucus to the bronchioles. Later they are found in the trachea, and being swallowed pass into the gut, where they attain their full maturity. The eradication of this disease depends upon the efficient disposal of night-soil, and upon the destruction of the adult parasites living within the body.

It has been estimated that over two million people in the Southern States were infected with this parasite in 1914. Knowledge of the life history has made it possible for this number to be greatly reduced in the past few years.

NOTES AND COMMENTS

The complete results of the Medical Society elections are as follows:—

Medical Society—President, J. R. Naden; Vice-Pres., W. B. Brebner; Sec.-Treas., A. G. Lambert; Ass't. Sec.-Treas., A. E. Young.

Medical Athletic Society—President, E. C. Noble (acclam.); Vice-Pres., F. M. Lively (acclam.); Sec.-Treas., S. Teskey (acclam.); Third Year Rep., G. C. Large; Second Year Rep., R. B. Robinson.

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2T4 Permanent Executive—President, E. P. Scarlett; Vice-Pres., J. E. Williams; Sec.-Treas., J. R. Neilson.

2T5 Class Executive—President, D. N. Henderson; Vice-Pres., J. H. Couch; Secretary, J. F. Walker; Treasurer, C. E. Knowlton; Varsity Reporter, J. H. Beasley.

2T6 Class Executive—President, H. H. Hyland; Vice-Pres., W. A. Oakes; Treasurer, S. S. Murray; Secretary, Miss F. M. Smith (accl.); Varsity Reporter, T. Bain; S.A.C. Rep., G. A. Dowsley; S.C.A. Reps., G. R. Balfour, F. J. Fleming.

2T7 Class Executive—President, W. A. Dinwoody; Vice-Pres., D. Curry; Secretary, Miss G. E. Mulock; Treasurer, L. A. Macklin; S.A.C. Rep., G. H. Rutherford; Varsity Reporter, C. E. Snelling.

2T8 Class Executive—President, T. H. Belt (accl.); Vice-Pres., R. A. Cleghorn; Treasurer, O. A. Kilpatrick; Secretary, Miss R. K. Haight; S.A.C. Rep., J. R. Robertson; Varsity Reporter, K. G. Gray; S.C.A. Reps., W. G. Brown, W. A. Guest.

2T9 Class Executive—President, L. E. Eckert; Vice-Pres., W. H. Saunders; Secretary, Miss M. V. Jackson; Treasurer, G. E. D. Wilson; S.A.C. Rep., W. A. McTavish; Varsity Reporter, A. H. Walker.

Daffydil Night

Daffydil, the annual Medical stunt night, was held on the evenings of Feb. 7th and 8th. There is no doubt this event is improving each year and is becoming one of the main functions of the term. The quality of the show was beyond reproach and Epistaxis was as popular as ever.

2T6 succeeded in winning the cup again this year with a well balanced production, "Toot and Come In." The girls secured second place with a very interesting skit.

Mr. R. Wagner of 2T6, the writer and director of the winning skit, deserves a great deal of credit both for this year's performance and that of last year. The members were: R. Wagner, Lorne Deeton, Roy Huggard, Jake Fine, S. D. Gordon, H. K. Moir, S. S. Murray, T. A. Sweet, P. Vale, F. J. Fleming, D. A. Irwin, C. E. Hassard.

The judges were: Dr. Shuttleworth, Dr. Oille, Dr. Wasteneys, Dr. Silverthorne, Dr. Wilson, Dr. W. B. Hendry.

A very successful dinner was held in the King Edward Hotel on the Saturday evening following the performance. The judges and members of the winning skit were guests of the Daffydil Committee.

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